

## **REMARKS**

Claims 1-47 are currently pending. Claims 31-36 and 42-47 have been withdrawn as directed to a non-elected invention. The present Response cancels claims 13-21, 32-34, 36, and 38-47; amends claims 1-3, 5-7, 10-12, 22-25, 30, and 37; amends withdrawn claims 31 and 35; and adds new claims 48-58.

### **I. Amendment of the Abstract**

The Office objected to the Abstract "because it contains legal phraseology such as comprises." The Abstract has been amended (a) to replace any "comprising" language with the comparable "containing" language throughout the Abstract, and (b) to conform the Abstract more closely to the claims as amended in the present Response.

### **II. Claim Amendments**

Claim 1 has been amended (a) to specify that the active pharmaceutical agent is reboxetine, or a pharmaceutically acceptable salt thereof; (b) to clarify that the starch has a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$ ; and (c) to specify that the solid fraction representative of the tablet is a solid fraction of 0.75 to 0.85. Support for these amendments can be found, for example, at paragraphs [0025], [0044], [0045], [0046], [0054], and [0080] of the specification; and Examples 1, 2 and 11 of the specification.

Claims 2 and 3 have been conformed to amended claim 1. Specifically, claims 2 and 3 have been amended (a) to delete the word "about" from the language "a tensile strength of at least about" as discussed further in Section III below; and (b) to specify that the solid fraction representative of the tablet is a solid fraction of 0.75 to 0.85. Support for these amendments can be found, for example, at paragraphs [0025] and [0054] of the specification.

Claims 5, 6, and 7 have been amended to clarify that the amount of starch present in the composition is expressed as a percent weight of the tablet. Support for these amendments can be found, for example, at paragraph [0061] of the specification.

Claims 10, 11, and 12 have been amended to clarify that the amount of hydrophilic polymer present in the composition is expressed as a percent weight of the tablet. Support for these amendments can be found, for example, at paragraph [0057] of the specification.

Claim 22 has been amended to specify that the active pharmaceutical agent is (S,S)-reboxetine, or a pharmaceutically acceptable salt thereof. Support for this amendment can be found, for example, at paragraphs [0044] and [0045] of the specification.

Claim 23 has been amended to depend from claim 22 and accordingly conformed to claim 22 as amended. Claim 23 still specifies that the active pharmaceutical agent is (S,S)-reboxetine succinate. Support for this amendment can be found, for example, at paragraphs [0044], [0045], and [0046] of the specification.

Claims 24 and 25 have been amended to depend from claim 1 rather than from cancelled claim 13 (which depended directly from claim 1).

Claim 30 has been amended to delete the word "about" from the language "a tensile strength of at least about" as discussed further in Section III below.

Withdrawn claim 31 has been amended (a) to specify that the active pharmaceutical agent is reboxetine, or a pharmaceutically acceptable salt thereof; and (b) to specify that the condition or disorder is a central nervous system condition or disorder. Support for this amendment can be found, for example, at paragraphs [0044], [0045], [0046], [0100], [0101], [0102] of the specification.

Withdrawn claim 34 has been amended to depend from claim 31 and accordingly conformed to claim 31 as amended. Claim 34 still specifies that the active pharmaceutical agent is (S,S)-reboxetine succinate. Support for this amendment can be found, for example, at paragraphs [0044], [0045], [0046], [0100], [0101], and [0102] of the specification.

Claim 37 has been amended (a) to specify that the active pharmaceutical agent is reboxetine, or a pharmaceutically acceptable salt thereof; (b) to delete the word "about" from the language "a tensile strength of at least about" as discussed further in Section III below; and (c) to specify that the solid fraction representative of the tablet is a solid fraction of 0.75 to 0.85. Support for this amendment can be found, for example, at paragraphs [0025], [0044], [0045], [0046], and [0054] of the specification.

New claims 48-58 depend from pending claims 2-13, respectively, and specify that the active pharmaceutical agent is (S,S)-reboxetine, or a pharmaceutically acceptable salt thereof. Support for these new claims can be found, for example, in original claims 1-12, 22 and 23; and at paragraphs [0044], [0045], and [0046] of the specification.

### **III. Claim Interpretation Objection**

The Office objected "that claim 1 as written can be interpreted in two different ways" with respect to whether the term "tensile strength" refers to the matrix comprising the hydrophilic polymer and the starch, or to the starch itself. The amendments to claim 1 now specify that the starch itself has a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$ .

### **IV. Section 112 Rejection**

The Office rejected claims 1-30 and 37-41 "under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the Office

asserted that the language in claims 1-3, 37 and 40 directed to "a tensile strength of at least about 0.15 (or 0.175 or 0.2) kN cm<sup>-2</sup>" is vague and indefinite. Claims 13-21 and 38-41 have been cancelled and the rejection of these claims is moot. To facilitate prosecution, however, the word "about" has been deleted from the language "a tensile strength of at least about" in claims 1-3, 30 and 37.

#### **V. Section 102(b) Rejection**

The Office rejected claims 1-3 and 13-14 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,036,948 (the "Kitamori Reference"). Since the present Response cancels claims 13 and 14, the rejection is moot as to these claims.

With respect to pending claims 1-3, these claims as amended now specify that the active pharmaceutical agent is reboxetine, or a pharmaceutically acceptable salt thereof. The Kitamori Reference only discloses compositions containing L-ascorbic acid. No compositions containing other pharmaceutical agents are disclosed. Since the Kitamori Reference does not disclose compositions containing reboxetine, or a pharmaceutically acceptable salt thereof, it does not anticipate claims 1-3.

#### **VI. Section 103(a) Rejection**

##### **A. Rejection of Claims 1-14, 20-22, 26, 29, 37 and 40**

The Office rejected claims 1-14, 20-22, 26, 29, 37 and 40 under 35 U.S.C. §103(a) as being unpatentable over the WO00/59477 (the "Vandecruys Reference"). Since the present Response cancels claims 13, 14, 20, 21, and 40, the rejection is moot as to these claims.

The present application addresses a formulation problem encountered with controlled release hydrophilic matrix tablets containing reboxetine, or a pharmaceutically acceptable salt thereof: conventional hydrophilic matrix tablets are

susceptible to "breakage and/or attrition during handling, especially in a high-speed tableting operation." Application, page 3, paragraph [0011]. Applicants have discovered that incorporating a starch having the required physical property (i.e., a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$ ) in the formulation used to prepare such hydrophilic matrix tablets yields tablets that: (a) are sufficiently bonded and retain a suitable hardness to avoid breakage and/or attrition during high-speed tableting operations, and (b) retain the disintegration properties needed to provide the desired sustained release profile suitable for once-daily administration. Each pending independent claim as amended now specifies that the starch used in the formulation has this nonobvious, required physical property:

1. A pharmaceutical composition in a form of an orally deliverable, sustained-release tablet comprising reboxetine, or a pharmaceutically acceptable salt thereof, dispersed in a matrix comprising a hydrophilic polymer and a starch, wherein the **starch has a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$  at a solid fraction of 0.75 to 0.85.**

\* \* \*

30. A pharmaceutical composition in a form of an orally deliverable tablet, comprising (S,S)-reboxetine succinate dispersed in a matrix comprising (a) HPMC in an amount of 35% to 50% by weight of the tablet and (b) a pregelatinized **starch having a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$  at a solid fraction of 0.8**, in an amount of 45% to 65% by weight of the tablet.

\* \* \*

37. A process for preparing a pharmaceutical composition according to Claim 1 in a form of an orally deliverable, sustained-release tablet, the process comprising selecting by a suitable test a **starch having a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$  at a solid fraction of 0.75 to 0.85**; admixing with the selected starch a hydrophilic polymer and reboxetine, or a pharmaceutically acceptable salt thereof, to provide a mixture wherein the reboxetine, or a pharmaceutically acceptable salt thereof, is dispersed in a matrix comprising the polymer and the starch; and compressing the mixture to form said tablet.

In contrast, the Vandecruys Reference addresses an entirely different formulation problem. The Vandecruys Reference addresses an unrelated formulation problem

encountered with conventional hydrophilic matrix tablets: the controlled release profile of such hydrophilic matrix tablets can change as the ionic strength of the release medium changes. According to the Vandecruys Reference, adding pregelatinized starch to the formulation used to prepare the tablets counters the effect of release medium ionic strength on the controlled release profile of the tablet. The pregelatinized starch apparently helps to maintain the tablet's ability to gel in the release medium and form the matrix network needed for controlled release. See, e.g., Vandecruys Reference, page 28, lines 31-34. The Vandecruys Reference further notes that a preferred form of pregelatinized starch is drum dried waxy maize starch and the most preferred weight percent of pregelatinized starch in the formulation is about 5%. Vandecruys Reference, page 11, lines 11-17.

The Office has expressly acknowledged that the Vandecruys Reference "is silent as to the tensile strength of the starch" and "does not specify selecting by a suitable test a starch." Nonetheless, the Office still maintains:

However, the starches utilized [sic] Vandecruys et al. are the same starches claimed in the instant application, pregelatinized starches. Therefore, absent evidence to the contrary, the examiner believes that the starches disclosed by Vandecruys et al. would have the same if not similar tensile strength.

The present application, however, expressly refutes this argument that all pregelatinized starches disclosed by the Vandecruys Reference would have the same or similar tensile strength:

[0082] Even among commercially available pregelatinized starches, the preferred type of starch for use in a composition of the invention, considerable variation exists in tensile strength. Pregelatinized starches not meeting the tensile strength criterion established herein are not readily identified without testing, for example by a method as disclosed above. Such pregelatinized starches are generally unsuitable for commercial scale manufacture of a sustained-release matrix tablet formulation of a water-soluble drug or prodrug, because of a problem as set forth immediately below.

Specification, page 23. The application then further describes the problems associated with the use of an unsuitable starch:

[0083] An uncoated tablet, or a tablet core prior to coating, comprising starch and a hydrophilic polymer acting as a matrix for a water-soluble drug or prodrug requires to have a certain minimum hardness in order to be able to resist breakage and/or attrition due to mechanical stresses imposed during a high-speed tableting operation (including all steps up to and including filling of the tablets into containers). The minimum acceptable hardness will depend on a number of factors, including the severity of the mechanical stresses, but is typically at least about 20 SCU, preferably at least about 22 SCU, more preferably at least about 24 SCU (about 17 kp).

[0084] **Hardness can be increased by increasing the compression force applied by the tablet press, but only up to a certain level. At least in the case of tablets as described herein, above a certain compression force, further increases in compression force give little or no further increase in tablet hardness. There is, in other words, a maximum hardness achievable by compression of a particular starch/hydrophilic polymer/active agent composition. A starch providing a maximum hardness inadequate to withstand the mechanical stresses of a high-speed tableting operation is unsuitable for the present purpose. As shown in Fig. 3, certain pregelatinized starches have been found to provide a maximum hardness of 20 SCU or less; these are now identified as starches having low tensile strength ( $0.1 \text{ kN cm}^{-2}$  or less according to the test method of the invention utilizing a dwell time of 90 seconds).**

[0085] Even if a maximum hardness of at least about 20 SCU is achievable, with a starch of low tensile strength it may be achievable only by use of extremely high compression forces. A requirement for such forces reduces speed and efficiency and increases cost of a tableting operation and is undesirable for these reasons.

Specification, page 23 (emphasis added).

In addition, this variability in the properties of starches was well-known in the art at the time the present application was filed:

Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. **These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application.** For example, amylose-rich maize starch has been studied as a potential tablet film-coating ingredient

Handbook of Pharmaceutical Excipients, Fourth Edition (Raymore C. Rowe, Editor), p. 608 (2003) (emphasis added). A copy of pages 603-614 of this Handbook of Pharmaceutical Excipients is attached to this Response for the convenience of the Office.

The examples of the present application further confirm this variability in both the physical properties of starches from different commercial lots and the physical properties of hydrophilic matrix tablets prepared from different commercial lots of starch:

(1) Example 1 reports the results of a triaxial tensile strength test on six commercially obtained lots of pregelatinized starch. These results reflected material variation in the tensile strength of the pregelatinized starches, ranging from 0.074 to 0.323 kN cm<sup>-2</sup>.

(2) Example 2 reports the results of a tensile strength test on the six commercially obtained lots of pregelatinized starch using a simplified test procedure. These results using the simplified test procedure likewise reflect material variation in tensile strength of the pregelatinized starches.

(3) Example 3 reports that tablets prepared from each of the six commercially obtained lots of pregelatinized starch were tested for hardness and resistance to erosion during a high-speed coating operation. The results of this testing are shown in Figure 3 of the specification. Two of the six pregelatinized starch lots were found to be unsuitable for tableting. Only the tablets prepared using pregelatinized starch having a tensile strength of at least 0.15 kN cm<sup>-2</sup> exhibited the desired hardness properties.

(4) Examples 11 and 12 collectively report that (S,S)-reboxetine succinate sustained-release tablets prepared using pregelatinized starch having a tensile strength of at least 0.15 kN cm<sup>-2</sup> retained the desired dissolution profile. The specific results of this testing are shown in Figure 5 of the specification.

The Vandecruys Reference contains no disclosure, teaching or suggestion that (a) tablet breakage and/or attrition is a problem during the preparation of a hydrophilic matrix tablet, particularly during high speed tableting operations; and (b) this problem is solved by including in the tablet a starch having a tensile strength of at least 0.15 kN cm<sup>-2</sup>. As discussed above, the mere addition of any starch to a formulation followed by

compression of that formulation into a tablet does not necessarily yield a tablet having sufficient hardness for use in a high speed tableting operation. The starch must also have the required physical property---a minimum tensile strength of at least  $0.15 \text{ kN cm}^{-2}$ . Tensile strength of the starch is not readily determined without suitable testing and can vary materially from starch lot to starch lot. The Vandecruys Reference simply provides no guidance to one of ordinary skill in the art that would make the claimed invention obvious.

Accordingly, claims 1-12, 22, 26, 29, and 37 are not obvious based on the Vandecruys Reference.

B. Rejection of Claims 15-19, 23-25, 30, 38-39, and 41

The Office rejected claims 15-19, 23-25, 30, 38-39, and 41 under 35 U.S.C. §103(a) as being unpatentable over the Vandecruys Reference in view of US2002/0010216 (the "Rogosky Reference"). Since the present Response cancels claims 15-19, 38-39, and 41, the rejection is moot as to these claims.

With respect to pending claims 23-25, these claims as amended now depend either directly or indirectly from, and incorporate the requirements of, claim 1. For the same reasons discussed above with respect to the rejection of claim 1, claims 23-25 likewise are not obvious based on the Vandecruys Reference. As previously discussed above, one of the nonobvious features of the claimed composition is its use of a controlled release matrix comprising a hydrophilic polymer and a starch wherein the starch has a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$  at a solid fraction of 0.75 to 0.85. Combining the teachings of the Vandecruys Reference and the Rogosky Reference does not alter this conclusion. Although the Rogosky Reference reports a composition comprising reboxetine and an antimuscarinic agent, the underlying deficiencies of the Vandecruys Reference when relied upon as a basis for the 103(a) rejection still remain.

With respect to pending claim 30, this claim as amended specifies, *inter alia*, a matrix comprising a hydrophilic polymer and a starch wherein the starch has a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$  at a solid fraction of 0.8. For the same reasons discussed above with respect to the rejection of claim 1, claim 30 likewise is not obvious based on the Vandecruys Reference. Combining the teachings of the Vandecruys Reference and the Rogosky Reference does not alter this conclusion. Although the Rogosky Reference reports a composition comprising reboxetine and an antimuscarinic agent, the underlying deficiencies of the Vandecruys Reference when relied upon as a basis for the 103(a) rejection still remain.

Accordingly, claims 23-25 and 30 are not obvious based on the Vandecruys Reference in view of the Rogosky Reference.

C. Rejection of Claims 27-28

The Office rejected claims 27-28 under 35 U.S.C. §103(a) as being unpatentable over the Vandecruys Reference in view of U.S. Patent No. 6,451,343 (the "Glinecke Reference").

Claims 27 and 28 depend indirectly from, and incorporate the requirements of, claim 1. For the same reasons discussed above with respect to the rejection of claim 1, claims 27 and 28 likewise are not obvious based on the Vandecruys Reference. Combining the teachings of the Vandecruys Reference and the Glinecke Reference does not alter this conclusion. As previously discussed above, one of the nonobvious features of the claimed composition is its use of a controlled release matrix comprising a hydrophilic polymer and a starch wherein the starch has a tensile strength of at least  $0.15 \text{ kN cm}^{-2}$  at a solid fraction of 0.75 to 0.85. Although the Glinecke Reference reports a controlled release oral dosage form having a release-controlling layer (and comprising a compound that is not reboxetine), the underlying deficiencies of the Vandecruys Reference when relied upon as a basis for the 103(a) rejection still remain.

Accordingly, claims 27 and 28 are not obvious based on the Vandecruys Reference in view of the Glinecke Reference.

**V. Provisional Obviousness-Type Double Patenting Rejection**

The Office has asserted a provisional obviousness-type double patenting rejection against: (a) pending claims 1-21 and 26-29 over claims 1-23 of copending Application Serial No. 10/626,166 (the "'166 Application"); (b) pending claims 1-21 and 37 over claims 1-23 of copending Application Serial No. 10/821,646 (the "'646 Application"); and (c) pending claims 26-29 over claims 1 and 13 of the '166 Application "in view of Vandecruys et al. or Glinecke et al."

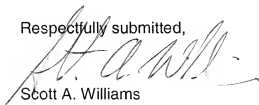
With respect to the rejection based on the '166 Application, Applicants believe that the claims as amended by the present Response clearly overcome this rejection. All pending claims now specify, or ultimately depend from a claim that specifies, that the composition comprises reboxetine, or a pharmaceutically acceptable salt thereof. In contrast, all claims of the '166 Application are directed to a composition comprising a water soluble salt of pramipexole. Accordingly, the claimed subject matter of the pending application is patentably distinct from the claimed subject matter of the '166 Application.

Applicants request clarification of the double patenting rejection based on the '646 Application. The '646 Application is titled "Method for accessing a personalized content on a home page hosted on a web site" and appears to completely unrelated to the claimed subject matter of the pending application.

Applicants respectfully submit that the present application is in condition for allowance. To advance the prosecution of the present application, however, the Office is invited to contact the undersigned at the telephone number provided below. If any

additional fees are required or an overpayment of fees is made, however, the Office is authorized to debit or credit our Deposit Account No. 16-1445, as necessary.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "S. A. Williams", written in dark ink.

Scott A. Williams  
Registration No. 39,876  
(314) 274-4474 (St. Louis)

Pfizer, Inc.  
P. O. Box 1027  
St. Louis, MO 63006

# Handbook of Pharmaceutical Excipients

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Edited by

**Raymond C Rowe**

BPharm, PhD, DSc, FRPharmS, CChem, FRSC, CPhys, MInstP

Senior Principal Scientist

AstraZeneca

Macclesfield, UK

**Paul J Sheskey**

BSc, RPh

Technical Service Leader

Water Soluble Polymers R&D

The Dow Chemical Company

Midland

MI, USA

**Paul J Weller**

BSc, MSc, CChem, MRSC

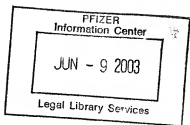
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# Starch

## 1 Nonproprietary Names

- BP: Maize starch  
Potato starch  
Rice starch  
Tapioca starch  
Wheat starch  
JP: Corn starch  
Potato starch  
Rice starch  
Wheat starch  
PhEur: Maydis amylum (maize starch)  
Solani amylum (potato starch)  
Oryzae amylum (rice starch)  
Tritici amylum (wheat starch)

### USP NF: Starch

Note that the USP NF 20 describes starch, in a single monograph, as being obtained from either the mature grain of corn, *Zea mays*, or of wheat, *Triticum aestivum*, or from tubers of the potato, *Solanum tuberosum*, or of tapioca, *Manihot utilissima*. The PhEur 2002 has individual monographs for each of these starches, except for tapioca starch, along with an additional monograph for rice starch, *Oryza sativa*. The BP 2001 similarly describes maize, potato, rice, tapioca (cassava), and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP 2001 similarly describes corn (maize), rice, potato and wheat starch in separate monographs. See also Section 18.

## 2 Synonyms

Amido; amidon; amilo; amylum; Aytex P; Fluflex W; Instant Pure-Cote; Melojel; Meritena; Paygel S5; Perfectamyl D6PH; Pure-Bind; Pure-Cote; Pure-Dent; Pure-Gel; Pure-Set; Purity 21; Purity 826; Tablet White.

See also Sections 1 and 18.

## 3 Chemical Name and CAS Registry Number

Starch [9005-25-8]

## 4 Empirical Formula

$(C_6H_{10}O_5)_n$

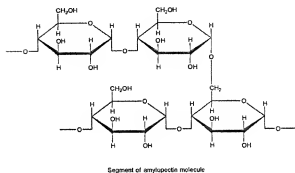
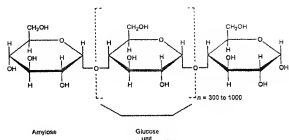
where  $n = 300-1000$ .

Starch consists of amylose and amylopectin, two polysaccharides based on  $\alpha$ -glucose. See also Sections 5 and 17.

## Molecular Weight

50 000-160 000

## 5 Structural Formula



## 6 Functional Category

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

## 7 Applications in Pharmaceutical Formulation or Technology

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.<sup>[1]</sup>

In tablet formulations, freshly prepared starch paste is used at a concentration of 5-25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3-15% w/w.<sup>[2-9]</sup> However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In

granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also starch when used as a disintegrant exhibits type II isotherms and has a high specific surface for water sorption.<sup>(10)</sup>

Starch has been investigated as an excipient in novel drug delivery systems for nasal,<sup>(11)</sup> oral,<sup>(12,13)</sup> peridental<sup>(14)</sup> and other site-specific delivery systems.<sup>(15)</sup>

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Therapeutically, rice starch-based solutions have been used in the prevention and treatment of dehydration due to acute diarrheal diseases.

## 8 Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

## 9 Pharmacopeial Specifications

See Table I.

## 10 Typical Properties

Acidity/alkalinity: pH = 5.5–6.5 for a 2% w/v aqueous dispersion of corn starch, at 25°C.

Compressibility: see Figure 1.

Density (bulk): 0.462 g/cm<sup>3</sup> for corn starch.

Density (tapped): 0.658 g/cm<sup>3</sup> for corn starch.

Density (true): 1.478 g/cm<sup>3</sup> for corn starch.

Flowability: 10.8–11.7 g/s for corn starch;<sup>(9)</sup> 30% for corn starch (Carr compressibility index);<sup>(16)</sup> Corn starch is cohesive and has poor flow characteristics.

Gelatinization temperatures: 73°C for corn starch; 72°C for potato starch; 63°C for wheat starch.

Moisture content: all starches are hygroscopic and rapidly absorb atmospheric moisture.<sup>(17,18)</sup> Approximate equilibrium moisture content values at 50% relative humidity are 11% for corn starch; 18% for potato starch; 14% for rice starch; and 13% for wheat starch. Between 30% and 80% relative humidity, corn starch is the least hygroscopic starch and potato starch is the most hygroscopic. Commercially available grades of corn starch usually contain 10–14% water. See also Figures 2 and 3.

Particle size distribution:

Corn starch: 2–32 µm

Potato starch: 10–100 µm

Rice starch: 2–20 µm

Tapioca starch: 5–35 µm

Wheat starch: 2–45 µm

Median diameter for corn starch is 17 µm and for wheat starch is 23 µm.

Solubility: practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about

5–10% at 37°C.<sup>(2,18)</sup> Polyvalent cations produce more swelling than monovalent ions, but pH has little effect.

Specific surface area:

0.41–0.43 m<sup>2</sup>/g for corn starch

0.12 m<sup>2</sup>/g for potato starch

0.27–0.31 m<sup>2</sup>/g for wheat starch

Swelling temperature:

65°C for corn starch

64°C for potato starch

55°C for wheat starch

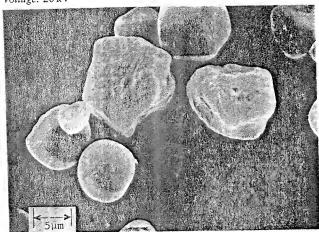
Viscosity (dynamic): 13.0 mPa s (13.0 cP) for a 2% w/v aqueous dispersion of corn starch at 25°C.

Table I: Pharmacopeial specifications for starch.

Test	JP 2001	PhEur, 2002	USPNF 20
Identification	+	+	+
Botanic	—	+	+
Characteristics			
Microbial limits	—	+	+
pH			
Corn starch	—	—	4.5–7.0
Potato starch	—	5.0–8.0	5.0–8.0
Tapioca	—	—	4.5–7.0
Wheat starch	—	5.0–8.0	4.5–7.0
Acidity	—	+	—
Loss on drying			
Corn starch	≤ 15.0%	≤ 15.0%	≤ 14.0%
Rice starch	≤ 15.0%	≤ 15.0%	—
Potato starch	≤ 18.0%	≤ 20.0%	≤ 14.0%
Tapioca	—	—	≤ 14.0%
Wheat starch	≤ 15.0%	≤ 15.0%	≤ 14.0%
Residue on ignition	—	—	≤ 0.5%
Sulfated ash			
Corn starch	≤ 0.5%	≤ 0.6%	—
Rice starch	≤ 1.0%	≤ 1.0%	—
Potato starch	≤ 0.5%	≤ 0.6%	—
Wheat starch	≤ 1.0%	≤ 0.6%	—
Iron			
Corn starch	—	—	≤ 0.002%
Potato starch	—	≤ 10 ppm	≤ 0.002%
Tapioca starch	—	—	≤ 0.002%
Wheat starch	—	≤ 10 ppm	≤ 0.002%
Organic volatile impurities	—	—	+
Oxidized substances			
Corn starch	—	—	≤ 0.002%
Potato starch	—	+	≤ 0.002%
Tapioca starch	—	—	≤ 0.002%
Wheat starch	—	+	≤ 0.002%
Sulfur dioxide			
Corn starch	—	—	≤ 0.008%
Potato starch	—	≤ 50 ppm	≤ 0.008%
Wheat starch	—	≤ 50 ppm	≤ 0.008%
Total protein			
Corn starch	—	—	—
Rice starch	—	—	—
Potato starch	—	≤ 0.1%	—
Wheat starch	—	≤ 0.3%	—
Foreign matter	—	+	—

## SEM: 1

Excipient: Corn starch  
 Manufacturer: Anheuser Busch  
 Lot No.: 96A-3 (67)  
 Magnification: 2400 x  
 Voltage: 20 kV



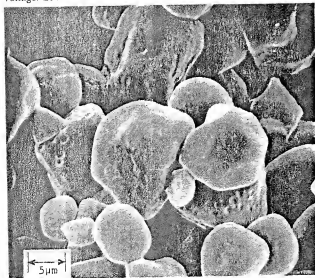
## SEM: 3

Excipient: Potato starch  
 Manufacturer: Starchem  
 Lot No.: 96A-5 (1179)  
 Magnification: 2400 x  
 Voltage: 20 kV



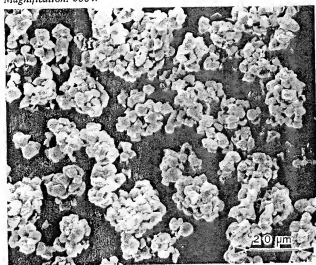
## SEM: 2

Excipient: Corn starch  
 Manufacturer: AE Staley Mfg. Co.  
 Lot No.: 96A-4 (G77912)  
 Magnification: 2400 x  
 Voltage: 20 kV



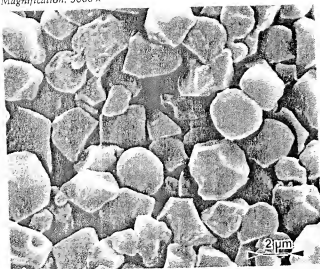
## SEM: 4

Excipient: Rice starch  
 Supplier: Matheson, Coleman & Bell  
 Magnification: 600 x



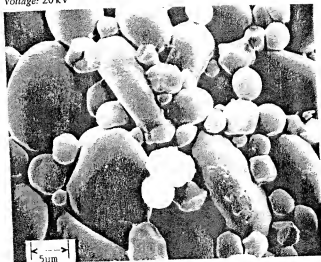
## SEM: 5

Excipient: Rice starch  
 Supplier: Matheson, Coleman & Bell  
 Magnification: 3000  $\times$



## SEM: 7

Excipient: Wheat starch (*Aytex P*)  
 Manufacturer: Henkel Corp.  
 Lot No.: 96A-2 (2919D)  
 Magnification: 2400  $\times$   
 Voltage: 20 kV



### 11 Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

Starch should be stored in an airtight container in a cool, dry place.

### 12 Incompatibilities

### 13 Method of Manufacture

Starch is extracted from plant sources through a sequence of processing steps involving coarse milling, repeated water washing, wet sieving, and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations.

### 14 Safety

Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets.

Starch is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material.<sup>(19)</sup> However, oral consumption of massive doses can be harmful owing to the formation of starch calculi, which cause bowel obstruction.<sup>(20)</sup> Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges. Contamination of surgical wounds with the starch glove powder used by surgeons has also resulted in the development of granulomatous lesions.<sup>(21)</sup>

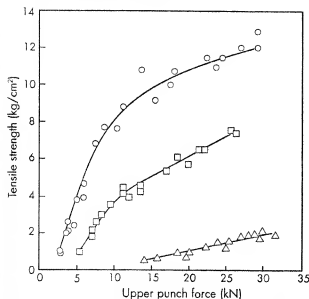
## SEM: 6

Excipient: Wheat starch (*Paygel SS*)  
 Manufacturer: Henkel Corp.  
 Lot No.: 96A-1 (2917D)  
 Magnification: 2400  $\times$   
 Voltage: 20 kV

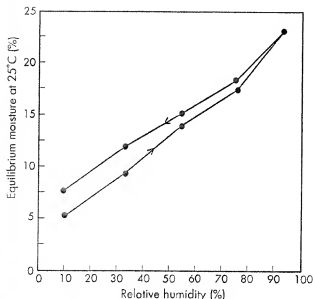


Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source.

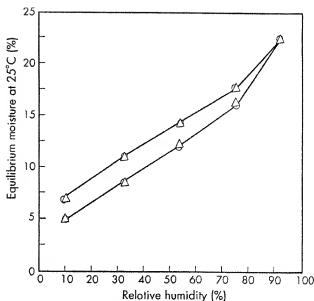
LD<sub>50</sub> (mouse, IP): 6.6 g/kg<sup>(22)</sup>



**Figure 1:** Compression characteristics of corn, potato and wheat starches.  
 □: Corn starch  
 ○: Potato starch  
 △: Wheat starch  
 Tablet machine: Manesty F; speed: 50 per min; weight: 490–510 mg. Strength test: Diametral compression between flat-faced rams. Upper ram stationary, lower moving at 66 µm/s.



**Figure 2:** Sorption-desorption isotherm of corn starch. Anheuser Busch; Lot #67



**Figure 3:** Sorption-desorption isotherm of wheat starch.  
 ○: Poeygel 55 [Henkel Corp.; Lot #2917D]  
 △: Aytex P [Henkel Corp.; Lot #2919D]

## 15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m<sup>3</sup> for total inhalable dust and 4 mg/m<sup>3</sup> for respirable dust.<sup>(23)</sup>

## 16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK.

## 17 Related Substances

Amylopectin; α-amylase; starch; pregelatinized; starch, sterilizable maize.

### Amylopectin

CAS number: [9037-22-3]

Comments: amylopectin is a branched D-glucan with mostly α-D-(1→4) and approximately 4% α-D-(1→6) linkages.

The EINECS number for amylopectin is 232-911-6.

### α-Amylase

CAS number: [9005-82-7]

Comments: amylase is a linear (1→4)-α-D-glucan.

## 18 Comments

Note that corn starch is also known as maize starch and that tapioca starch is also known as cassava starch.

Whereas the USPNF 20 specifies that starch should be produced from corn, potato, tapioca, or wheat, the BP 2001

also permits starch to be produced from rice. In tropical and subtropical countries where these starches may not be readily available, the BP 2001 additionally permits the use of tapioca starch, subject to additional requirements.

Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application.

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### 21 Author

G Rowley.

### 22 Date of Revision

10 March 2002.

# Starch, Pregelatinized

## 1 Nonproprietary Names

BP: Pregelatinized starch  
PhEur: Amylum pregelificatum  
USPNF: Pregelatinized starch

## 2 Synonyms

Compressible starch; *Instastarch*; *Lycatab C*; *Lycatab PGs*; *Merigel*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST 200*; *Spress B820*; *Starch 1500 G*; *Tablitz*; *Unipure LD*; *Unipure WG220*.

## 3 Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

## 4 Empirical Formula Molecular Weight

$(C_6H_{10}O_5)_n$ , where  $n = 300-1000$ .

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USP NF 20 does not specify the botanical origin of the original starch, but the PhEur 2002 (Suppl 4.1) specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. See also Starch and Section 13.

## 5 Structural Formula

See Starch.

## 6 Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

## 7 Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,<sup>(1,2)</sup> and disintegrant.<sup>(3)</sup>

In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression processes.<sup>(4-14)</sup> In such processes, pregelatinized starch is self-lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.<sup>(15)</sup>

Pregelatinized starch may also be used in wet granulation processes.<sup>(16)</sup> See Table I.

Table I: Uses of pregelatinized starch.

Use	Concentration (%)
Diluent (hard gelatin capsules)	5-75
Tablet binder (direct compression)	5-20
Tablet binder (wet granulation)	5-10
Tablet disintegrant	5-10

## 8 Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e., no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin show characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g., *Starch 1500G* and *Sepistab ST200*) show retention of birefringence patterns typical of unmodified starch granules.

## 9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for pregelatinized starch.

Test	PhEur 2002 (Suppl 4.1)	USPNF 20
Identification	+	+
pH (10% w/v slurry)	4.5-7.0	4.5-7.0
Iron	≤20 ppm	≤0.002%
Oxidizing substances	+	+
Sulfur dioxide	≤50 ppm	≤0.008%
Microbial limits	+	+
Loss on drying	≤15.0%	≤14.0%
Residue on ignition	—	≤0.5%
Foreign matter	+	—
Sulfated ash	≤0.6%	—
Organic volatile impurities	—	+

## 10 Typical Properties

Acidity/alkalinity: pH = 4.5-7.0 for a 10% w/v aqueous dispersion.

Angle of repose: 40.7°<sup>(6)</sup>

Compressibility: see Starch.

Density (bulk): 0.586 g/cm<sup>3</sup>

Density (tapped): 0.879 g/cm<sup>3</sup>

Density (true): 1.516 g/cm<sup>3</sup>

Flowability: 18-23% (Carr compressibility index)<sup>(17)</sup>

Moisture content: pregelatinized maize starch is hygroscopic.<sup>(14,18,19)</sup> See also Figure 1.

Particle size distribution: 30–150  $\mu\text{m}$ , median diameter 52  $\mu\text{m}$ .

For partially pregelatinized starch, greater than 90% through a US #100 mesh (149  $\mu\text{m}$ ); and less than 0.5% retained on a US #40 mesh (420  $\mu\text{m}$ ).

**Solubility:** practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water-soluble matter for partially pregelatinized starch is 10–20%.

**Specific surface area:**

0.26  $\text{m}^2/\text{g}$  (Colorcon)

0.18–0.28  $\text{m}^2/\text{g}$  (Roquette Ltd)

**Viscosity (dynamic):** 8–10  $\text{mPa}\cdot\text{s}$  (8–10 cP) for a 2% w/v aqueous dispersion at 25°C.

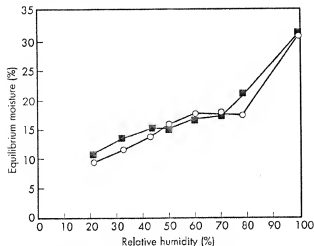


Figure 1: Pregelatinized starch sorption-desorption isotherm.  
○: Sorption. ■: Desorption.

### 11 Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

### 12 Incompatibilities

### 13 Method of Manufacture

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–72°C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range.

Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying takes place. Partially pregelatinized starch is produced by subjecting moistened starch to mechanical pressure. The resultant material is ground and the moisture content is adjusted to specifications.

### 14 Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of pregelatinized starch may be harmful.

See Starch for further information.

### 15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10  $\text{mg}/\text{m}^3$  for total inhalable dust and 4  $\text{mg}/\text{m}^3$  for respirable dust.<sup>(20)</sup>

### 16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions, and tablets). Included in nonparenteral medicines licensed in the UK.

### 17 Related Substances

Starch; starch, sterilizable maize.

### 18 Comments

A low-moisture grade of pregelatinized starch, *Starch 1500 LM* (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.<sup>(15)</sup>

*Sepistab ST200* is described as an agglomerate of starch granules consisting of native and pregelatinized corn starch.<sup>(21)</sup>

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## 21 Author

G Rowley.

## 22 Date of Revision

13 June 2002.

# Starch, Sterilizable Maize

## 1 Nonproprietary Names

USP: Absorbable dusting powder

## 2 Synonyms

*Bio-sorby*; double-dressed, white maize starch; *Fluidamid R444P*; *Keoflo ADP*; *Meritena*; modified starch dusting powder; *Pure-Dent B851*; starch-derivative dusting powder; sterilizable corn starch.

## 3 Chemical Name and CAS Registry Number

Sterilizable maize starch

## 4 Empirical Formula Molecular Weight

$(C_4H_{10}O_5)_n$  where  $n = 300$ –1000.

Sterilizable maize starch is a modified corn (maize) starch that may also contain up to 2.0% of magnesium oxide.

See also Starch.

## 5 Structural Formula

See Starch.

## 6 Functional Category

Lubricant for surgeons' and examination gloves; vehicle for medicated dusting powders.

## 7 Applications in Pharmaceutical Formulation or Technology

Sterilizable maize starch is a chemically or physically modified corn (maize) starch that does not gelatinize on exposure to moisture or steam sterilization. Sterilizable maize starch is primarily used as a lubricant for examination and surgeons' gloves. It is also used as a vehicle for medicated dusting powders.

## 8 Description

Sterilizable maize starch occurs as an odorless, white, free-flowing powder. Particles may be rounded or polyhedral in shape.

## 9 Pharmacopeial Specifications

See Table 1.

Table 1: Pharmacopeial specifications for sterilizable maize starch

Test	USP 25
Identification	+
Stability to autoclaving	+
Sedimentation	+
pH (1 in 10 suspension)	10.0–10.8
Loss on drying	≤ 12%
Residue on ignition	≤ 3%
Magnesium oxide	≤ 2.0%
Heavy metals	≤ 0.001%

## 10 Typical Properties

Acidity/alkalinity: pH = 9.5–10.8 for a 10% w/v suspension at 25 °C.

Density: 1.48 g/cm<sup>3</sup>

Density (bulk): 0.47–0.59 g/cm<sup>3</sup>

Density (tapped): 0.64–0.83 g/cm<sup>3</sup>

Flowability: 24–30% (Carr compressibility index)<sup>(1)</sup>

Moisture content: 10–15%

Particle size distribution: 6–25 µm; median diameter is 16 µm.

Solubility: very slightly soluble in chloroform and ethanol (95%); practically insoluble in water.

Specific surface area: 0.50–1.15 m<sup>2</sup>/g

## 11 Stability and Storage Conditions

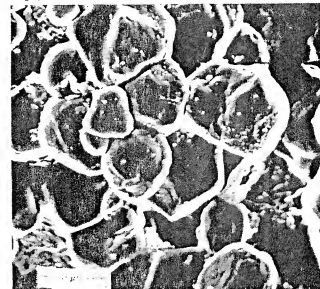
Sterilizable maize starch may be sterilized by autoclaving at 121 °C for 20 minutes, by ethylene oxide, or by irradiation.<sup>(2)</sup>

### SEM: 1

Excipient: Sterilizable maize starch

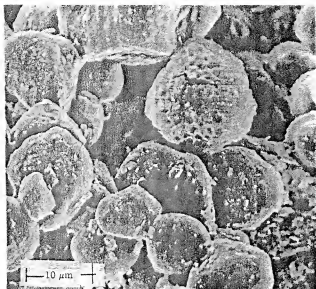
Manufacturer: Corn Products

Magnification: 2000 ×



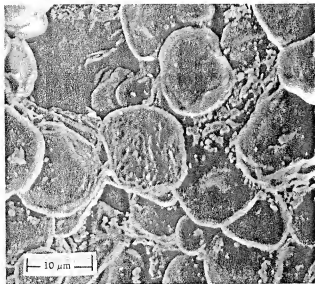
## SEM: 2

Excipient: Sterilizable maize starch  
 Manufacturer: Biosorb  
 Magnification: 2000 x



## SEM: 3

Excipient: Sterilizable maize starch  
 Manufacturer: J & W Starches Ltd  
 Magnification: 2000 x



Sterilizable maize starch should be stored in a well-closed container in a cool, dry place.

## 12 Incompatibilities

## 13 Method of Manufacture

Corn starch (maize starch) is physically or chemically modified by treatment with either phosphorus oxychloride or epichlorohydrin so that the branched-chain and straight-chain starch polymers crosslink. Up to 2.0% of magnesium oxide may also be added to the starch.

See also Starch.

## 14 Safety

Sterilizable maize starch is primarily used as a lubricant for surgeons' gloves and as a vehicle for topically applied dusting powders.

Granulomatous reactions and peritonitis at operation sites have been attributed to contamination with surgical glove powders containing sterilizable maize starch.<sup>(3,4)</sup> The use of excessive quantities of sterilizable maize starch on surgeons' gloves should therefore be avoided.

See also Starch.

## 15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m<sup>3</sup> for total inhalable dust and 4 mg/m<sup>3</sup> for respirable dust.<sup>(5)</sup>

## 16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets and topical preparations). Included in nonparenteral medicines licensed in the UK.

## 17 Related Substances

Starch; starch, pregelatinized.

## 18 Comments

## 19 Specific References

- 1 Carr RL. Particle behaviour storage and flow. *Br Chem Eng* 1970; 15: 1541-1549.
- 2 Kelsey JC. Sterilization of glove powder by autoclaving. *Mon Bull Minist Health* 1962; 21: 17-21.
- 3 Neely J, Davis JD. Starch granulomatosis of the peritoneum. *Br Med J* 1971; 3: 625-629.
- 4 Michaels L, Shah NS. Dangers of corn starch powder [letter]. *Br Med J* 1973; 2: 714.
- 5 Health and Safety Executive. *EHA0/2002: Occupational Exposure Limits 2002*, Sudbury: Health and Safety Executive, 2002.

**20 General References**

- El Saadany RMA, El Saadany FM, Foda YH. Degradation of corn starch under the influence of gamma irradiation. *Stärke* 1976; **28**: 208-211.
- Greenwood CT. The thermal degradation of starch. *Adv Carbohydr Chem Biochem* 1967; **22**: 483-515.
- Greenwood CT. Starch. *Adv Cereal Sci Technol* 1976; **1**: 119-157.

**21 Author**

G Rowley.

**22 Date of Revision**

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